# Niaviolides, New Macrocyclic Sesquiterpenes Secreted by Males of the African Butterfly *Amauris niavius*

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**Keywords:** Configuration determination / Macrolides / Natural products / Pheromones / Terpenoids

The abdominal androconial organs ("hairpencils") of the African butterfly *Amauris niavius* (Danainae) emit a complex scent bouquet consisting of previously described aromatic compounds, terpenoids, fatty acids, and hydrocarbons. This work reports the identification of two major sesquiterpenes, each possessing a unique 13-membered macrolide ring, originating from an α,ω-oxidation pattern of the sesquiterpene backbone. To the best of our knowledge, sesquiterpene macrolides have not been found before in nature. The structure elucidation of the two compounds, which we propose to call niaviolide (**3**) and epoxyniaviolide (**4**), by NMR and GC/MS experiments is presented, together with their subsequent synthesis. Finally, the absolute configuration of natural **4** was determined to be (*S*,*S*) by stereoselective synthesis and chiral gas chromatography.



## Introduction

The milkweed butterfly *Amauris niavius* (Lepidoptera, Danainae) lives in African forest habitats. Like other danaines, males possess dual androconial organs (male-specific glandular structures generally producing courtship pheromones): hindwing scent patches and protrudable abdominal hairpencils, the latter being employed in close-range courtship behavior.[1,2] The hairpencil chemicals comprise a complex bouquet,[3] probably necessary to overcome the difficulty of visual intraspecific recognition caused by the involvement of *A. niavius* in complex mimicry rings.[1−3]

The hairpencil volatiles of *A. niavius* have been investigated repeatedly. The scent bouquet consists predominately of aromatic compounds, terpenoids, hydrocarbons, and fatty acids. Meinwald et al. identified the dihydropyrrolizine danaidone and 3,4-dimethoxyacetophenone as the major hairpencil components and reported the presence of further unidentified components.[4] A reinvestigation showed that part of this mixture consists of straight-chain alkanes, 2,5-dialkyltetrahydrofurans, and some other minor components.[3]

Here we report the identification and synthesis of two additional major compounds, **I** and **II** (compounds N10 and N11 in ref.[3]), of the hairpencil secretion. Additionally, the absolute configuration of the natural chiral compound **II** was determined by its asymmetric synthesis, followed by GC experiments with a chiral stationary phase.

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## Results and Discussion

Hairpencils and wing glands of field-collected *A. niavius* were extracted with pentane, as described in the Exp. Sect. The obtained extracts were investigated by GC-MS (Figure 1), revealing the presence of two unknown compounds, **I** and **II**.

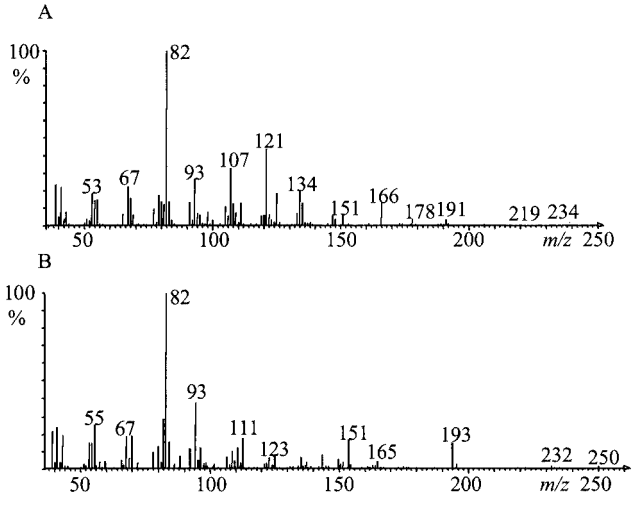



Figure 1. Mass spectra of the natural components: A) **I**; B) **II**

The mass spectra of the two compounds, shown in Figure 1, exhibit molecular ions at $m/z$ = 234 and 250, respectively. High-resolution mass spectrometry revealed their molecular compositions to be $C_{15}H_{22}O_2$ and $C_{15}H_{22}O_3$. These data suggested that the compounds were sesquiterpenes, which was supported by their characteristic terpenoid fragmentation patterns. The more abundant compound **II** was isolated by preparative GC on a packed glass column. Several microreactions were then performed, both with total hairpencil extract and with the isolated compound, to obtain information on the functional groups in both compounds. During hydrogenation of isolated **II**, 2 equiv. of hydrogen were taken up. The hydrogenation product consisted of at least three diastereomers, because a GC analysis showed the presence of three different peaks with very similar mass spectra. It follows that the hydrogenation product must have three or more stereocenters, which could be explained by the presence of two trisubstituted double bonds and one stereocenter in the original molecule **II**. Compound **II** did not react with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA), but reduction with LAH resulted in several compounds, which took up three trimethylsilyl groups after treatment with MSTFA. Transesterification of **II** with sodium methoxide in methanol resulted in the formation of a hydroxy methyl ester. These results are consistent with a lactone structure containing either an oxo or an epoxy group and two double bonds in **II**.

Compound **I** took up 3 equiv. of hydrogen, was silylated twice after reduction, and also formed a hydroxy methyl ester after transesterification. These derivatives of **I** were identified in the derivatized extracts. Compound **I** therefore seems to have a structure similar to that of **II**, lacking the oxo or epoxy group, but with an additional double bond. Compound **II** thus seems to be the oxidized form of **I**.

NMR experiments were performed with the purified sample of **II**. Since the amount of isolated **II** was less than 1 mg, only one- and two-dimensional $^1$H NMR experiments were performed (Figure 2). Each of the double bonds contained one proton. The isolated proton ($\delta$ = 5.6 ppm) seems to be in an α-position next to a carbonyl group, because of the low-field shift. The signal at $\delta$ = 4.8 ppm is a triplet and the proton appears to be located at a double bond next to a $CH_2$ group. The diastereotopic oxymethylene hydrogen atoms ($\delta \approx$ 4.2 ppm) are isolated, as no further coupling to other protons was detected. Finally, a dd at $\delta$ = 2.8 ppm was interpreted as a signal of an oxirane proton next to another $CH_2$ group.

From these data it was concluded that both **I** and **II** are 13-membered macrolides, derived from ω-oxidized farnesoic acid (Scheme 1). The location of the epoxy group was uncertain, so structure **III** was also consistent with the obtained data.

To verify the suggested structures and to determine the configurations of their double bonds, a combinatorial synthesis commencing from the isomeric mixture of farnesols was carried out (Scheme 2). Farnesol was quantitatively oxidized to farnesal with PDC. After $MnO_2$/KCN/MeOH oxidation and esterification to methyl farnesoate (75%),[5] allylic oxidation with $SeO_2$/*t*BHP yielded a mixture of methyl 12-hydroxyfarnesoates (**2**) (54%).[6] The esters **2** were saponified and the acids were cyclized under Corey/Nicolaou conditions with $PPh_3$ and dithiodipyridine in boiling toluene (33%).[7] A mixture of three major macrolides **3** in a ratio of (*Z*,*E*,*E*)-**3**/(*Z*,*Z*,*E*)-**3**/(*E*,*E*,*E*)-**3** = 41:33:26 was obtained, accompanied by minor amounts of other regioisomers.

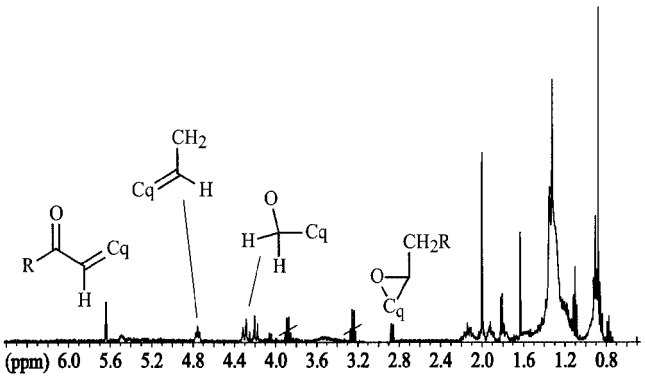
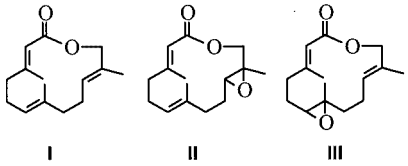
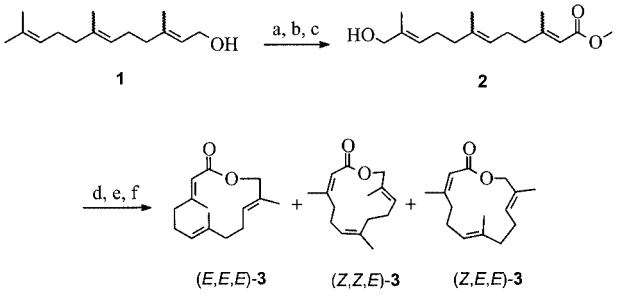



Figure 2. $^1$H NMR (400 MHz, $C_6D_6$, 25 °C) of **II**




Scheme 1. Structures of **I**, **II**, and **III**

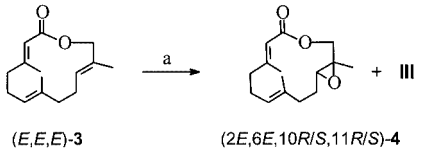



Scheme 2. a) PDC, dichloromethane, 0 °C to 25 °C; b) $MnO_2$, KCN, HOAc, MeOH; c) $SeO_2$, *t*BHP, dichloromethane, 0−25 °C; d) KOH, MeOH, $H_2O$, 50 °C; e) $PPh_3$, $(C_5H_4NS)_2$, toluene, 25 °C; f) toluene, reflux

Chromatographic purification of the crude mixture of **3** and subsequent NOESY experiments on the isolated products allowed the configurations of the isomers to be determined. The presence of coupling between an olefinic proton and the neighboring $CH_3$ group showed that double bond to possess (*Z*) configuration, the absence of coupling characterizing the (*E*) configuration. Pure (*Z*,*E*,*E*)-**3** and a mixture of inseparable (*Z*,*Z*,*E*)- and (*E*,*E*,*E*)-**3** were thus obtained.

Because of the moderate yield of the cyclization by the Corey–Nicolaou procedure, other macrolactonization methods were tried. Mukaiyama[8] prepared macrolides directly from their ω-hydroxycarboxylic acids by the use of a combination of 4-(trifluoromethyl)benzoic anhydride, a catalytic amount of active titanium(IV) salts, and chlorotrimethylsilane. These milder conditions furnished only a low yield (12%) of the same macrolides. Kitagawa and co-workers used NaH in toluene.[9] They also synthesized macrolides derived from (*E*,*E*)-farnesol, but with the carbonyl group at C-12 rather than at the C-1 position as in our work. Again, the yield of **3** was low (9%). All three methods showed different compositions of the three isomers. In essence, in comparison with the Corey/Nicolaou method, only minor amounts of the desired (*E*,*E*,*E*)-**3** could be obtained by the other methods [(*Z*,*E*,*E*)-**3**/(*Z*,*Z*,*E*)-**3**/(*E*,*E*,*E*)-**3**: Corey–Nicolaou: 41:33:26; Kitagawa: 62:27:11; Mukaiyama: 15:62:23].

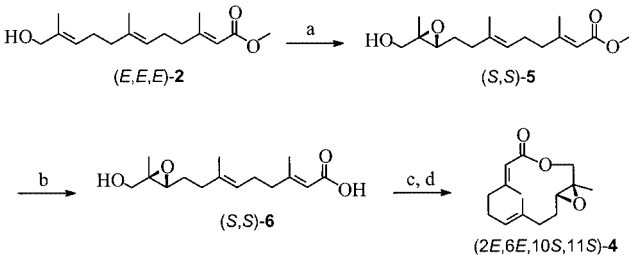
Comparison of the fragmentation patterns and the retention times of the synthetic products with those of the natural compound showed **I** to be identical with (*E*,*E*,*E*)-**3**, for which we propose the name niaviolide. Pure niaviolide [(*E*,*E*,*E*)-**3**] was then obtained by the described synthetic route by starting from (*E*,*E*)-farnesol instead of an isomeric mixture.




Scheme 3. Conversion of niaviolide [(*E*,*E*,*E*)-**3**] into epoxyniaviolides [(2*E*,6*E*,10*R*/*S*,11*R*/*S*)-**4**] and [(2*E*,6*R*/*S*,7*R*/*S*,10*E*)-**4**] by use of *m*CPBA in dichloromethane, 0 °C

The proposed structures **II** or **III** were synthesized by epoxidation of (*E*,*E*,*E*)-**3** with *m*CPBA. Because of steric hindrance and electronic effects, the 10,11-double bond was attacked preferentially, forming **II** as the main product (75%), while the 6,7-epoxide **III** was formed only in minor amounts. No product containing an epoxy group in the 2,3-position was obtained. This is in agreement with previous findings on the epoxidation of methyl farnesoate.[10] Comparison of the analytical data for the synthetic and natural products confirmed our initial considerations and showed compound **II** to be the (2*E*,6*E*,10*R*/*S*,11*R*/*S*)-macrolide **4**, which we propose to call epoxyniaviolide.

Finally, the absolute configuration of **II** was determined. Enantiomers of **4** were synthesized by Sharpless epoxidation (Scheme 4).[11] The (*S*,*S*)-oxirane **5** was obtained from the already synthesized methyl 12-hydroxyfarnesoate (**2**) in 96% yield by use of (L)-(+)-diisopropyl tartrate, Ti(O*i*Pr)$_4$, and *t*BHP in the presence of molecular sieves, according to the Sharpless mnemonic scheme.[11] Saponification and further cyclization of the (*S*,*S*)-acid **6** under Corey–Nicolaou conditions furnished the macrolide (*S*,*S*)-**4** in 25% yield.




Scheme 4. Enantioselective synthesis of (*S*,*S*)-**4**: A) Ti(O*i*Pr)$_4$, (L)-(+)-diisopropyl tartrate, *t*BHP, dichloromethane, −20 °C; b) KOH, MeOH, $H_2O$; c) $PPh_3$, $(C_5H_4NS)_2$, toluene, 25 °C; d) toluene, reflux

Gas chromatographic analysis of the synthetic epoxymacrolide (*S*,*S*)-**4** and the natural androconial extract on a chiral cyclodextrin phase showed that the natural epoxyniaviolide (**4**) possesses the (*S*,*S*) configuration. The natural compound is enantiomerically pure, while the synthetic compound had an *ee* of 91% (Figure 3).

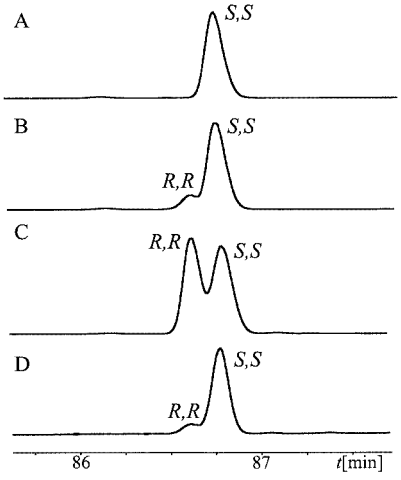



Figure 3. Gas chromatographic investigation of natural and synthetic **4** on a chiral Hydrodex-6-TBDMS stationary phase, $T$ = 125 °C isotherm; A) isolated natural **4**, B) co-injection of natural and *rac*-**4**, C) *rac*-**4**, D) (*S*,*S*)-**4**

To the best of our knowledge, the niaviolides are the first sesquiterpenoid α,ω-macrolides to be found in nature. Further analysis showed that **3** and **4** occur in both androconial organs, the hindwing patches as well as in the hairpencils.

## Conclusion

The structure of two previously unknown terpenoid macrolides present in the androconial extract of the African danaine butterfly *Amauris niavius* was elucidated by the use of microreactions and NMR and GC/MS experiments and confirmed by synthesis. Niaviolide (**3**) is derived from ω-oxidized (*E*,*E*,*E*)-farnesoic acid, whereas the more highly oxidized macrolide **4** (epoxyniaviolide) has the same carbon skeleton, but contains an epoxide in the 10,11-positions.

The absolute configuration of the naturally occurring macrolide **4** was determined as (*S*,*S*). Interestingly, epoxidation of terpenoids is also used by other danaines to produce scent compounds.[12] While the function of the compounds remains to be elucidated, their uniqueness and occurrence in the androconia indicate a prominent role in the complex courtship communication of *A. niavius*.

## Experimental Section

**General Remarks:** $^1$H and $^{13}$C NMR spectra were obtained with Bruker AC 200 and AMX 400 instruments. $CDCl_3$ was used in NMR experiments if not mentioned otherwise; the internal standard was tetramethylsilane or solvent ($CD_2Cl_2$, δ = 5.32 and 53.7 ppm). GC-MS was carried out with a Hewlett−Packard model 5973 mass-selective detector connected to a Hewlett−Packard model 6890 gas chromatograph. Analytical GLC analyses were performed with a CE instruments GC 8000 gas chromatograph equipped with a flame ionization detector and split/splitless injection. The optical rotatory power was measured with a Dr Kernchen Propol Digital Automatic polarimeter. Chiral GC separations were performed on a hydrodex-6-TBDMS phase (50 m, 0.25 mm i.d., Macherey & Nagel). All reactions were carried out under nitrogen in oven-dried glassware. Dry solvents: dry toluene was distilled from Na, dichloromethane from $CaH_2$, THF from K and Na. All other chemicals were commercially available (Fluka, Aldrich) and were used without further treatment. All reactions were monitored by thin layer chromatography (TLC) carried out on Macherey−Nagel Polygram SIL G/UV$_{254}$ silica plates and viewed by use of heat gun treatment with 10% molybdatophosphoric acid in ethanol. Column chromatography was performed on Merck silica gel 60 (70−200 mesh). Preparative GC was performed with a Carlo−Erba Fractovap gas chromatograph equipped with a 2-m glass column (2 mm i.d.) filled with Carbowax 20 M. Nitrogen was used as carrier gas. Butterflies were collected in Kenya, mostly near Kwale (Coast Province). Additional butterflies were bought from Kipepo Project, Kenya. The hairpencils were protruded by manual pressure, removed with forceps, touched on absorbent paper to remove excess hemolymph and stored under pentane (Merck, Suprasolv) in vials. In Germany, samples were stored at −70 °C until workup. Wing patches were cut out with scissors and treated in the same way.

**Microreactions:** Silylations were performed by addition of MSTFA (20 μL) to a $CD_2Cl_2$ solution of **II** (about 20 μL) in a closed-cap vial. After the mixture had been heated at 50 °C for 30 min, the solvent and excess MSTFA were removed with a gentle stream of nitrogen. The residue was taken up in $CH_2Cl_2$ and analyzed by GC-MS. Reduction with LAH[13] and transesterification with sodium methoxide[14] were performed as described earlier.

**(2*E*,6*E*)-Farnesal:** (2*E*,6*E*)-Farnesol (**1**, 4 mL, 16 mmol) was dissolved in dichloromethane (140 mL) and cooled to 0 °C. Pyridinium dichromate (9 g, 24 mmol) was then added in portions and the mixture was stirred for 24 h. Afterwards, diethyl ether (100 mL) was added and the reaction mixture was filtered through a short silica plug. The solvent was removed and the product was obtained quantitatively and sufficiently pure for the next step. NMR data are consistent with reported data.[15] MS (70 eV): *m*/*z* (%) = 41 (53), 69 (100), 81 (22), 84 (56), 93 (10), 136 (10), 220 (3).

**Methyl (2*E*,6*E*)-Farnesoate:**[5] (*E*,*E*)-Farnesal (2.62 g, 11.8 mmol) was added dropwise to a suspension of KCN (3.4 g, 51.8 mmol), acetic acid (0.8 mL, 15.8 mmol), activated $MnO_2$ (19.5 g, 224 mmol), and methanol (45 mL). The reaction mixture was stirred at room temperature for 24 h. This mixture was then filtered through a short silica plug and the solvent was removed. The residue was diluted with water (50 mL) and extracted three times with diethyl ether. The combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated. The crude product (2.24 g, 8.9 mmol, 75%) was sufficiently pure for characterization and further work. NMR data are identical to the reported data.[16] MS (70 eV): *m*/*z* (%) = 41 (43), 69 (100), 79 (10), 81 (27), 114 (43), 121 (33).

**Methyl (2*E*,6*E*,10*E*)-12-Hydroxyfarnesoate [(*E*,*E*,*E*)-2]:**[6] A solution of methyl (*E*,*E*)-farnesoate (1.75 g, 6.9 mmol) in dry dichloromethane (4 mL) was added dropwise to an ice-cold mixture of $SeO_2$ (420 mg, 3.5 mmol), anhydrous *tert*-butyl hydroperoxide solution (4 mL, 22 mmol, 5.5 M in nonane), and dry dichloromethane (100 mL). The mixture was stirred in the dark overnight while being allowed to warm to room temperature. It was then diluted with dichloromethane (50 mL) and washed with saturated $NaHCO_3$ solution, followed by brine. The organic layer was dried with $MgSO_4$ and filtered, and the dichloromethane was removed. Ethanol (20 mL) and $NaBH_4$ (26 mg, 0.8 mmol) were added to the residue at 0 °C, and the mixture was stirred for 45 min. It was then concentrated in vacuo, and water (50 mL) was added to the residue. The aqueous phase was extracted three times with diethyl ether. The combined ethereal extracts were dried with $MgSO_4$ and the solvent was removed. The crude product was purified by flash chromatography on silica, with pentane/diethyl ether (4:1) as eluent. Some of the methyl (*E*,*E*)-farnesoate starting material (320 mg, 1.3 mmol, 18%) could also be reisolated. Yield: 1.0 g (3.7 mmol, 54%; 66% excluding recovered starting material). NMR data identical to reported data.[6]

**(2*E*,6*E*,10*E*)-12-Hydroxyfarnesenic Acid:** Methyl hydroxyfarnesoate (**2**, 300 mg, 1.1 mmol) was dissolved in methanol (20 mL), and KOH solution (3 mL, 2 N) was added. The mixture was stirred at 50 °C for 3 d. After concentration in vacuo, brine (25 mL) was added. The mixture was extracted once with diethyl ether, and the aqueous layer was then acidified with HCl (1 N). After extraction with diethyl ether (three times), the combined organic phases were dried with $MgSO_4$ and the solvent was evaporated to yield the hydroxy acid, sufficiently pure for the next step (186 mg, 0.7 mmol, 64%). $^1$H NMR: δ = 1.61 (s, 3 H, $CH_3$), 1.66 (s, 3 H, $CH_3$), 2.01−2.23 (m, 8 H), 2.17 (s, 3 H, $CH_3$), 3.99 (s, 2 H, $CH_2$), 5.08−5.14 (m, 1 H, CH), 5.35−5.39 (m, 1 H, CH), 5.68 (s, 1 H, CH) ppm. $^{13}$C NMR: δ = 13.7 (q), 16.0 (q), 19.1 (q), 25.8 (t), 26.0 (t), 39.2 (t), 41.1 (t), 68.8 (t), 115.1 (d), 123.0 (d), 125.8 (d), 134.7 (s), 135.9 (s), 162.8 (s), 171.4 (s) ppm. $C_{15}H_{24}O_3$ (252.4): calcd. C 71.39, H 9.59; found C 71.42, H 9.42.

**(2*E*,6*E*,10*E*)-Niaviolide [(*E*,*E*,*E*)-3]:** (2*E*,6*E*,10*E*)-12-Hydroxyfarnesoic acid (150 mg, 0.6 mmol) was added at room temperature to a solution of 2,2′-dithiodipyridine (230 mg, 1 mmol) and triphenylphosphane (270 mg, 1 mmol) in dry toluene (1 mL). The mixture was stirred for 5 h and was then diluted with dry toluene (10 mL). This solution was added by syringe pump over 15 h to boiling toluene (150 mL) and the mixture was then boiled for additional 10 h. The toluene was removed in vacuo and the crude product was purified by silica flash chromatography (pentane/diethyl ether, 19:1). Yield: 43 mg (0.2 mmol, 33%). $^1$H NMR ($CD_2Cl_2$): δ = 1.35 (s, 3 H, $CH_3$), 1.47 (s, 3 H, $CH_3$), 1.95 (d, *J* = 1 Hz, 3 H, $CH_3$,), 2.00−2.42 (m, 8 H), 4.46 (d, *J* = 1 Hz, 2 H,

$CH_2$), 4.91 (t, $J$ = 7 Hz, 1 H, CH), 5.14 (m, 1 H, CH), 5.67 (m, 1 H, CH) ppm. $^{13}$C NMR: δ = 13.7 (q), 14.4 (q), 17.9 (q), 22.6 (t), 26.1 (t), 39.5 (t), 40.9 (t), 68.5 (t), 118.2 (d), 123.1 (d), 125.6 (d), 129.9 (s), 135.4 (s), 159.6 (s), 166.9 (s) ppm. MS (70 eV): *m*/*z* (%) = 39 (25), 41 (24), 67 (23), 82 (100), 83 (14), 93 (27), 107 (33), 121 (42). HRMS: calcd. for $C_{15}H_{22}O_2$ 234.1620; found 234.1612.

**Mixture of Niaviolide Isomers:** The reaction was performed as described for (*E*,*E*,*E*)-**3**, ω-hydroxyfarnesoic acid derived from the isomeric mixture of farnesol being used as starting material. Yield: 116 mg [0.31 mmol, 31%; mixture of (*E*,*E*,*E*)-**3**/(*Z*,*Z*,*E*)-**3**/(*Z*,*E*,*E*)-**3** = 26:33:41].

**(2*Z*,6*Z*,10*E*)-Niaviolide [(*Z*,*Z*,*E*)-3]:** Compound (*Z*,*Z*,*E*)-**3** was obtained as an inseparable mixture with (*E*,*E*,*E*)-**3**. $^1$H NMR ($CD_2Cl_2$): δ = 1.62 (s, 3 H, $CH_3$), 1.62 (d, $J$ = 1 Hz, 3 H, $CH_3$), 1.81 (d, $J$ = 1 Hz, 3 H, $CH_3$), 2.00−2.42 (m, 8 H), 4.42 (s, 2 H, $CH_2$), 5.04 (t, $J$ = 7 Hz, 1 H, CH), 5.46 (dt, $J$ = 2, $J$ = 7 Hz, 1 H, CH), 5.51 (d, $J$ = 1 Hz, 1 H, CH) ppm. $^{13}$C NMR: δ = 15.4 (q), 23.3 (q), 25.6 (q), 27.2 (t), 28.2 (t), 31.7 (t), 35.1 (t), 67.8 (t), 117.9 (d), 126.2 (d), 129.1 (d), 130.8 (s), 134.2 (s), 156.4 (s), 166.9 (s) ppm. MS (70 eV): *m*/*z* (%) = 39 (49), 41 (49), 53 (33), 54 (29), 55 (24), 67 (46), 68 (32), 77 (27), 79 (37), 80 (32), 81 (24), 82 (100), 83 (22), 91 (33), 93 (68), 94 (26), 105 (28), 107 (51), 111 (40), 121 (95), 135 (60), 166 (21) ppm. HRMS: calcd. for $C_{15}H_{22}O_2$ 234.1620; found 234.1606.

**(2*Z*,6*E*,10*E*)-Niaviolide [(*Z*,*E*,*E*)-3]:** $^1$H NMR ($CD_2Cl_2$): δ = 1.41 (s, 3 H), 1.52 (s, 3 H), 1.81 (d, $J$ = 1 Hz, 3 H, $CH_3$), 1.90−2.13 (m, 8 H), 4.35 (s, 2 H, $CH_2$), 4.85−4.92 (m, 1 H, CH), 5.03−5.06 (m, 1 H, CH), 5.69 (s, 1 H, CH) ppm. $^{13}$C NMR ($CD_2Cl_2$): δ = 14.2 (q), 14.2 (q), 22.9 (t), 23.9 (q), 25.6 (t), 31.8 (t), 39.6 (t), 66.5 (t), 118.0 (d), 123.5 (d), 125.0 (d), 129.1 (s), 130.2 (s), 156.7 (s), 166.6 (s) ppm. MS (70 eV): *m*/*z* (%) = 39 (36), 41 (33), 53 (34), 54 (18), 55 (21), 67 (36), 68 (31), 79 (26), 80 (35), 82 (88), 91 (22), 93 (43), 105 (30), 107 (38), 111 (42), 121 (100), 151 (24), 166 (50) ppm. HRMS: calcd. for $C_{15}H_{22}O_2$ 234.1620; found 234.1603.

**(2*E*,6*E*,10*R*/*S*,11*R*/*S*)-Epoxyniaviolide [(2*E*,6*E*,10*R*/*S*,11*R*/*S*)-4]:** A solution of (*E*,*E*,*E*)-**3** (20 mg, 0.08 mmol) in dichloromethane (2 mL) was added to a mixture of *m*-chloroperbenzoic acid (33 mg, 0.1 mmol) in dichloromethane (5 mL) at 0 °C. The reaction was monitored by TLC. After completion, saturated $NaHCO_3$ solution (4 mL) was added. The layers were separated and the aqueous one was extracted three times with dichloromethane. The combined organic extracts were dried with $MgSO_4$ and the solvent was removed. The crude product was purified by flash chromatography with pentane/diethyl ether (9:1) as eluent. The minor 6,7-epoxide could not be isolated. Yield: 16 mg (0.06 mmol, 75%). $^1$H NMR ($C_6D_6$): δ = 1.11 (s, 3 H, $CH_3$), 1.14−1.20 (m, 1 H, $CH_2$), 1.32 (s, 3 H, $CH_3$), 1.38−1.46 (m, 1 H, $CH_2$), 1.77−1.82 (m, 2 H, $CH_2$), 1.84−2.17 (m, 4 H), 2.00 (d, $J$ = 1 Hz, 3 H, $CH_3$), 2.86 (dd, $J$ = 2, $J$ = 8 Hz, 1 H, CH), 4.18 (d, $J$ = 12 Hz, 1 H, $CH_2$), 4.29 (d, $J$ = 12 Hz, 1 H, $CH_2$), 4.76 (br. t, $J$ = 3 Hz, 1 H, CH), 5.64 (s, 1 H, CH) ppm. $^{13}$C NMR ($C_6D_6$): δ = 14.6 (q), 14.8 (q), 17.5 (q), 24.7 (t), 25.8 (t), 38.1 (t), 40.2 (t), 57.5 (d), 65.0 (t), 118.8 (d), 126.3 (d), 167.1 (s) ppm. MS (70 eV): *m*/*z* (%) = 39 (27), 41 (28), 43 (23), 55 (29), 67 (20), 81 (27), 82 (100), 93 (35). HRMS: calcd. for $C_{15}H_{22}O_3$ 250.1569; found 250.1585. MS data for the 6,7-epoxide **III** (70 eV): *m*/*z* (%) = 39 (34), 41 (41), 43 (32), 53 (23), 55 (29), 67 (27), 69 (24), 77 (16), 79 (24), 81 (37), 82 (100), 91 (21), 93 (27), 105 (21), 107 (21), 109 (20), 121 (20), 133 (22), 147 (28).

**(−)-Methyl (2*E*,6*E*,10*S*,11*S*)-10,11-Epoxy-12-hydroxyfarnesoate [(*S*,*S*)-5]:** (L)-(+)-Diisopropyl tartrate (19 mg, 0.08 mmol) and $Ti(OiPr)_4$ (16 μL, 0.05 mmol) were added at 0 °C to powdered activated molecular sieves (50 mg, 4 Å) and dry dichloromethane (5 mL). The mixture was cooled to −20 °C, and *tert*-butyl hydroperoxide solution (0.38 mL, 2.2 mmol, 5.5 M anhydrous in nonane) was added. After the mixture had been stirred for 20 min, (*E*,*E*,*E*)-**2** (280 mg, 1.0 mmol) in dry dichloromethane (0.5 mL) was added. The solution was stirred at −20 °C for 3 h. Water (0.5 mL) was then added at 0 °C and the mixture was stirred at room temperature for 45 min. An NaOH solution (0.8 mL, 30%) saturated with NaCl was added, and the phases separated. The aqueous phase was extracted three times with dichloromethane and the combined organic layers were dried with $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography (pentane/diethyl ether, 1:1), providing pure epoxyfarnesoate (*S*,*S*)-**5**. Yield: 270 mg (0.96 mmol, 96%). $^1$H NMR: δ = 1.28 (s, 3 H, $CH_3$), 1.61−1.73 (m, 2 H, $CH_2$), 1.63 (d, $J$ = 1 Hz, 3 H, $CH_3$), 2.07−2.21 (m, 6 H), 2.16 (d, $J$ = 1 Hz, 3 H, $CH_3$), 3.01 (t, $J$ = 6 Hz, 1 H, CH), 3.55 (d, $J$ = 12 Hz, 1 H, $CH_2$), 3.57 (d, $J$ = 12 Hz, 1 H, $CH_2$), 3.69 (s, 3 H, $CH_3$), 5.13−5.14 (m, 1 H, CH), 5.67 (d, $J$ = 1 Hz, 1 H, CH) ppm. $^{13}$C NMR: δ = 14.2 (q), 16.0 (q), 18.8 (q), 25.8 (t), 26.7 (t), 36.2 (t), 40.7 (t), 50.8 (q), 59.7 (d), 60.8 (s), 65.4 (t), 115.3 (d), 123.7 (d), 135.1 (s), 159.8 (s), 167.2 (s) ppm. $[\alpha]_D^{20}$ = −11.4 (*c* = 2.2, diethyl ether). $C_{16}H_{26}O_4$ (282.4): calcd. C 68.06, H 9.28; found C 67.84, H 9.29.

**(2*E*,6*E*,10*S*,11*S*)-10,11-Epoxy-12-hydroxyfarnesoic Acid [(*S*,*S*)-6]:** Methyl epoxyfarnesoate [(*S*,*S*)-**5**, 100 mg, 0.36 mmol] was dissolved in methanol (7 mL), and KOH solution (1 mL, 2 N) was added. The mixture was stirred at 60 °C overnight and concentrated in vacuo, and brine (4 mL) was added to the residue. The mixture was extracted once with diethyl ether, and the aqueous layer was then acidified with HCl (1 N). After extraction with diethyl ether (three times) the combined organic phases were dried with $MgSO_4$ and the solvent was evaporated to yield the crude hydroxy acid (*S*,*S*)-**6** (91 mg, 0.34 mmol, 94%), which was directly used in the next step. $^1$H NMR: δ = 1.28 (s, 3 H, $CH_3$), 1.62−1.72 (m, 2 H), 1.63 (s, 3 H, $CH_3$), 2.00−2.29 (m, 6 H), 2.16 (d, $J$ = 1 Hz, 3 H, $CH_3$), 2.91−3.13 (m, 1 H, CH), 3.57 (d, $J$ = 12 Hz, 1 H, $CH_2$), 3.68 (d, 1 H, $CH_2$), 4.98 (s, 1 H, OH), 4.97−5.30 (m, 2 H, CH, OH), 5.68 (s, 1 H, CH) ppm. $^{13}$C NMR: δ = 14.1 (q), 19.0 (q), 20.9 (q), 25.7 (t), 26.5 (t), 36.2 (t), 40.9 (t), 60.0 (d), 61.5 (s), 65.3 (t), 115.2 (d), 123.3 (d), 135.1 (s), 162.3 (s), 170.0 (s) ppm.

**(+)-(2*E*,6*E*,10*S*,11*S*)-Epoxyniaviolide [(*S*,*S*)-4]:** The preparation was performed analogously to that of (*E*,*E*,*E*)-**1**, starting from (*S*,*S*)-epoxyhydroxyfarnesoic acid [(*S*,*S*)-**6**]. Yield: 35 mg (0.15 mmol, 25%). For NMR and MS data see (2*E*,6*E*,10*R*/*S*,11*R*/*S*-**4**). HRMS: calcd. for $C_{15}H_{22}O_3$ 250.1569; found 250.1579. The *ee* values were determined by GC on a chiral hydrodex-6-TBDMS phase, operated isothermally at 125 °C; $T_r$(*S*,*S*) = 86.89 min, $T_r$(*R*,*R*) = 86.65 min. *ee* = 91%. $[\alpha]_D^{20}$ = +3.0 (*c* = 1, diethyl ether).

## Acknowledgments

Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der chemischen Industrie is gratefully acknowledged, as well as the Kenyan research permit to M. B. We thank Prof. W. Francke for many helpful discussions in the early stage of the project.

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Received October 11, 2002
[O02565]